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<b>(21) International Application Number:</b> PCT/US82/01593 <b>(22) International Filing Date:</b> 8 November 1982 (08.11.82)  <b>(31) Priority Application Number:</b> 318,607 <b>(32) Priority Date:</b> 9 November 1981 (09.11.81) <b>(33) Priority Country:</b> US  <b>(71)(72) Applicant and Inventor:</b> BAZZANO, Gail, Sansone [US/US]; 4506 Avron Boulevard, Metairie, LA 70002 (US).  <b>(74) Common Representative:</b> BAZZANO, Gail, Sansone; 4506 Avron Boulevard, Metairie, LA 70002 (US).  <b>(81) Designated States:</b> AT (European patent), BE (European patent), BR, CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent).		<b>Published</b> <i>With international search report.</i> <i>With amended claims.</i>
<b>(54) Title:</b> THE USE OF RETINOIDS AND MINOXIDIL (2,4-DIAMINO-6-PIPERIDINO-PYRIMIDINE-3-OXIDE) TO INCREASE THE RATE OF GROWTH OF HUMAN SCALP HAIR AND TO TREAT CERTAIN TYPES OF ALOPECIAS  <b>(57) Abstract</b>  Use of retinoids and minoxidil (2,4-diamino-6-piperidino-pyrimidine-3-oxide) to increase the rate of hair growth and to prolong the anagen phase of the hair cycle and to treat certain types of alopecia.		

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The Use of Retinoids and Minoxidil (2,4,-diamino-6-piperidino-pyrimidine-3-oxide) to Increase the Rate of Growth of Human Scalp Hair and to Treat Certain Types of Alopecias.

#### Background of the Invention:

##### 1. Field of the Invention

This invention relates to the use of retinoids and their derivatives in combination with minoxidil (2,4,-diamino-6-piperidino-pyrimidine-3-oxide) in order to increase the rate of growth of human scalp hair and to treat certain types of alopecias.

##### 2. Description of the Prior Art

A normal characteristic of human hair growth in most individuals is that it diminishes with age. Both the rate of growth of the hair and the length of the growing cycle are reduced. This condition is common to all individuals with rare exception and must be differentiated from true male pattern alopecia which is a distinct clinical entity associated in certain individuals with the production of the male sex hormone, testosterone and its derivatives, particularly dihydrotestosterone.

Many factors may influence the rate of hair growth including race, sex, age, region, season of the year, nutrition and hormones (Myers and Hamilton, 1951, Hamilton, 1958, Yano, 1936, Maeda, 1938, Troter, 1923, Pinkus, 1924, and Ono, 1963). In the past, many attempts have been made to alter the course of male pattern alopecia without success.

#### Detailed Description of the Invention:

This invention concerns the use of certain retinoids, including all-trans retinoic acid and its metabolites and other retinoid compounds in combination with minoxidil in order to increase the rate of hair growth and to treat various alopecias. The present inventor has applied for U.S. and PCT patents #235,169 and #PCT-US-81-00338 respectively on February 17, 1981, on the use of retinoids in the promotion of hair

growth. All-trans retinoid acid has been shown to cause elevated DNA synthesis in keratinocytes in cell culture. All-trans retinoic acid can also be shown to increase the turnover time of epidermal cells in cell culture experiments as well as in vivo experiments with human subjects. The present inventor has discovered that the cells of the hair follicle including the papillae can be stimulated by retinoids including all-trans retinoic acid. When tested experimentally, the retinoids caused the cells of the dermal papillae and the cells of the root sheath to incorporate more tritiated thymidine into DNA and to reproduce at a more rapid rate than untreated cells from other hair follicles. This stimulation by the retinoid compounds ultimately causes the entire hair follicle to become more activated and the mitotic index as measured by thymidine-H<sup>3</sup> incorporation into DNA to rise. Therefore, the individual scalp hairs can be shown to grow at an increased rate and the anagen phase is prolonged.

A major problem in influencing alopecia is to revascularize the area of alopecia and initiate the primary new hair growth. All-trans retinoic acid and its derivatives and the other retinoid compounds have been shown to give excellent percutaneous absorption and to be very active on the keratinizing cells of the skin, including the hair follicle, however, it is difficult for retinoids alone to revascularize the area of the pilosebaceous apparatus.

Studies have shown that minoxidil, a potent antihypertensive medication and peripheral vasodilator can increase the rate of hair growth on the body when taken systemically, particularly in areas of the limbs and facial areas, primarily due to vasodilatory properties. Further studies have suggested that minoxidil may be effective in initiating and promoting vellus hair growth on the scalp in individuals with alopecia, however, minoxidil is not able to sustain the growth of terminal hairs from vellus hairs on the scalp; and in the majority of subjects with alopecia even pronounced vellus hair growth on the scalp is not initiated or sustained by the topical application of minoxidil nor by the systemic administration.

The mechanism by which minoxidil exerts its effect is



believed to be revascularization and by its vasodilatory properties, however, vasodilation alone is not sufficient stimulus for hair growth, particularly in an area affected by alopecia. The present inventor has applied for patent PCT-US-81-00338 on March 12, 1981, and has shown that certain retinoids can increase the rate of hair growth in both males and females and can prolong the anagen phase of the hair cycle thereby converting vellus to terminal follicles. The mechanism of action of the retinoid compounds is believed to be through the initiation and activation of increased cell differentiation, i.e., compounds which of themselves can initiate the differentiation of cells of the pilosebaceous apparatus which eventually form the hair follicle and become terminal hairs.

Because of the advanced state of scalp thinning and atrophy of the pilary portion of the pilosebaceous apparatus, it is difficult to initiate hair growth from areas of advanced male pattern alopecia. Certain of the retinoid compounds sustain and promote hair growth in areas where some hair is present to some extent. However, in very advanced cases of complete or total male pattern alopecia, certain retinoids may not produce sufficient new hair growth.

The present application is for the use of certain retinoid compounds with minoxidil. The stimulatory actions of both compounds can promote each others effect, i.e., synergism, retinoids can initiate cell growth and differentiation (not initiated by minoxidil) and minoxidil can promote the vasodilatory action not readily obtained with the retinoids. While neither compound alone can have profound effects on advanced alopecias, in combination the compounds are very effective as promoters of new hair growth in areas of alopecia.

The net result of application of minoxidil and retinoids is initiating and production of new hair growth and conversion of vellus to terminal hair growth, i.e., the increase in size from a vellus to a terminal hair and the continued and more prolonged maintenance of the hair in the anagen phase.

As noted previously, this effect is obtained not merely

as the addition of two compounds but as synergism, i.e., the combination of these substances in the present invention produces an effect which cannot be produced by either compound separately under conditions of its use and, therefore, represents a major advance in the treatment of alopecia.

As used herein, the term retinoid denotes retinol, retinal, retinyl esters as well as retinoic acid and its esters, derivatives and normal metabolites. The terminal group may be oxidized, reduced, esterified, etc. The alkali metal (sodium, potassium, etc.) and alkaline earth metal (magnesium, calcium, etc.) salts are also included herein. As used herein, the term minoxidil (generic name) denote the following chemical compound and its active derivatives: 2,4,-diamino-6-piperidino-pyrimidine-3-oxide, as in U.S. patents #3,461,461 and #4,139,619.

The pharmaceutical or cosmetic or veterinary preparation of the present invention can be prepared by the conventional techniques for the preparation of lotions, creams, conditioners or shampoos for the scalp or veterinary preparation for pelts. Included also are preparations which can be administered orally.

In addition to the active retinoids and minoxidil of this invention, the various preparations can contain any conventional pharmaceutically acceptable or cosmetically acceptable inert or pharmacodynamically active additives. For example, the lotions may be prepared using various forms of alcohols or other solubilizers such as glycols, or esters. The conditioners may contain the normally acceptable commercially produced compounds such as cetyl alcohol, ceteareth-5,-20 hydrations, hydrolyzed animal protein, glycol stearate, amodimethicone, paraffin, mineral oil, etc. (These are only given as examples, and are not meant to be inclusive.) The topical compounds may also contain various oils including essential fatty acids such as vitamins, steroid hormones including progesterone, estradiols, thyroid, as well as analogues, and certain prostaglandins and prostaglandin analogues.

The topically applied lotions, creams, and conditioners, etc. will vary according to the standard art with regard to the amounts of other hydrophilic and hydrophobic containing

ingredients including emulsifiers, so that either an oily, semi-oily or oil free product may be obtained. The shampoos may contain any of the conventionally used detergents or soaps and any other compounds used by those familiar with the art. Oil based shampoos are included in these formulations.

The oral preparations may be tablets, liquids, capsules, etc. The pharmaceutically acceptable substances commonly used as preservatives, stabilizers, moisture retainers, emulsifiers, etc. can be present in these preparations. Conventionally acceptable antioxidants such as tocopherols, N-methyl  $\alpha$ -tocopheramine, butylated hydroxyanisole and butylated hydroxytoluene, can be also incorporated in the preparations described in this invention.

The dosages in which the retinoids and minoxidil are administered can be varied with the route of administration and the requirements of the subjects.

The topical treatments may consist of lotions, creams, conditioners, shampoos, oil treatments, etc. with from 0.001 to 2% weight of all-trans retinoic acid or derivatives, or other retinoids, as the preferred dosages in the described compositions and with dosages of from .01% to 30% minoxidil in suitable vehicles for percutaneous adsorption.

The oral pharmaceutical preparations may be administered at a daily dose of from 0.25 mg to 2 mg per kilogram of body weight or retinoids and from 0.01 to 10.0 mg/kg body weight for minoxidil.

In order to examine the specific action of the retinoids and minoxidil in increasing the rate of hair growth, several types of experiments were performed. The microcapillary method was used in each case to measure the rate of hair growth. Other methods of dye staining and hair growth measurements were also undertaken. In addition, the method of Ebling et al, Journal of Investigative Dermatology, November 1981, was used to study the conversion of vellus to terminal hairs by microscopy.

In Table I is described the results of studies using male and female subjects. The all-trans retinoic acid and minoxidil in lotion form was applied topically or as described in the table and hair growth rates were assessed along with

transformation from vellus to terminal hairs. (See separate pages for TABLES).

In Table II is described the results of studies using male and female subjects. The ethyl ester of all-trans retinoic acid was applied topically described in the table and a control non-treated area was utilized for comparison.

In fur bearing animals, the rate of fur growth, length of hair, thickness of hair and molting season are controlled by many factors including season, light (wavelength) periodicity, temperature, hormonal factors and nutrition. Controlling all of these variables is impossible, however, animals were selected and areas over the hind quarters were shave in 2 inch diameter circular areas. In some of the animals the areas were treated topically with all-trans retinoic acid and in other animals the retinoid was administered orally in animal chow. Some of the animals served as their own controls, using treated and non-treated areas.

In fur bearing animals, the guard hairs and the pile hairs differ in thickness, length and growth rate. In the rabbits studies, the guard hairs averaged 34 mm and the pile hairs 30 mm in length. The effect of topical application of all-trans retinoic acid was to increase the rate of new hair growth. An effect on the non-shaved fur bearing areas treated with topical all-trans retinoic acid in lotion form, was a decrease in the shedding or molting of fur. The mean rate of hair (fur) growth from treated shaved areas was 0.3 mm/day for 3 rabbits (mean) while in non-treatment shaved areas it averaged 0.2 mm/day (mean of 3 rabbits).

The effect could also be demonstrated in domestic cats and dogs; the same type of experimental procedures were used. The most striking effect in long haired dogs and cats was the retardation of molting or hair shedding. Long haired dogs and cats tended to retain more hair in the anagen phase and there was approximately 50% less shedding during the treatment periods. Both methods of administration were satisfactory. Either topical lotion or cream treatment or systemic treatment by inclusion in animal chow was satisfactory. The daily dosage for animals was 20 mg per kilogram per day in chow or 10 to 15 mg applied topically.



Commercially important fur bearing animals were also used for experimentation. Two male minks were closely clipped over the back hind quarters. The animals were treated on one hind quarter and the other was used as the control. The capillary method for measuring hair growth was used for these studies. The animals were treated by two different methods. The animals were either fed the retinoid in their chow or they were administered the retinoid topically. The daily dose was 20 mg per kg body weight per day in animal chow or 5 mg per day applied topically. The results of these experiments showed that the rate of growth of new pelt was increased approximately 30% by the retinoid treatment.

Experiments using birds (canaries and parakeets) showed that inclusion of the all-trans retinoic acid or the ethyl ester of all-trans retinoic acid in bird food at a dosage of 30 mg per kilogram bird weight per day retarded the molting process.

The following Examples illustrate the present invention. The methods of administration may vary by lotion, cream, ointment, pill, supplement to chow, coating for seeds, etc. These Examples are only meant to be illustrative and do not limit the mode of administration nor the ingredients which can be admixed to the present invention, nor the amounts which may be used.

## Example I

Lotion formulation for the topical  
administration

% wt to wt

Active ingredients:

I. All-trans retinoic acid	0.1
II. Minoxidil:	3.0
Ethanol	q.s. to 100.0
Propylene glycol	5.0
Butylated hydroxytoluene	0.1
Safflower oil	1.0
$\alpha$ -tocopherol acetate	0.5
Stabilizer	0.1

## Example II

Cream conditioner for Topical Administration

Active ingredients:

I. All-trans retinoic acid	1.0
II. Minoxidil	10.0
Distilled water	q.s. to 100.0
Cetrimonium Chloride	5.0
Cetyl alcohol	4.0
Ethanol	4.0
Butylated hydroxytoluene	1.0
Hydrolyzed animal protein	0.5
Methylparaben, propylparaben	0.1
Stabilizer	0.1

## Example III

All-trans retinoic acid 0.1 gram and 10 grams of minoxidil are dissolved in 100 ml of acetone, and the solution admixed with 900 g of USP grade hydrophilic ointment to a

uniform consistency; one gram of butylated hydroxy-toluene is added. The water washable cream ointment thus prepared consists of 0.1% retinoic acid and 10% minoxidil

#### Example IV

Tablets for oral administration

Minoxidil	10 mg.
Active ingredients all-trans retinoic acid	25 mg.
Lactose	52 mg.
Cornstarch	20 mg.
Microcrystalline cellulose	40 mg.
Talc	2.5 mg.
Magnesium stearate	0.5 mg.

The active ingredients are mixed with lactose and granulated using a corn starch paste. The remainder of the above adjuvants was then admixed therein and the mass was tableted. The tablets were then tableted. The tablets were then coated with a water-soluble or water-swellaable lacquer.

The same formulation can also be used and gelatin can be added to make beadlets. These beadlets are then coated with a lacquer. The beadlets and animal chow can be mixed to the desired dosage level.

The above formulation can also be used in the powdered form for mixing with bird seed and the bird seed can then be sprayed with lacquer.

Liquids, syrups or other formulations can be made consistent with the pharmaceutical art.

RESULTS USING LOTION CONTAINING  
ALL-TRANS RETINOIC ACID 0.1%  
AND MINOXIDIL 3%

TABLE I

<u>Subject</u> <u>Sex</u>	<u>Age</u>	<u>Dosage</u> <u>Lotion</u>	<u>Form</u> <u>of</u> <u>Dosage</u>	<u>Treat-</u> <u>ment</u> <u>Time</u>	<u>mm/day</u> <u>Control</u> <u>Rate</u>	<u>mm/day</u> <u>Treat-</u> <u>ment</u> <u>Rate of</u> <u>Growth</u>	<u>% of conversion</u> <u>from vellus to</u> <u>terminal per</u> <u>sq. cm. during</u> <u>treatment</u>
M	37	10 ml/ day	Topical lotion applied to Scalp	2 mths.	0.23	0.30	11%
M	62	"	"	"	0.21	0.29	22%
M	38	"	"	"	0.35	0.42	35%
F	43	"	"	"	0.37	0.39	13%
F	38	"	"	"	0.31	0.35	18%
F	64	"	"	"	0.24	0.29	17%

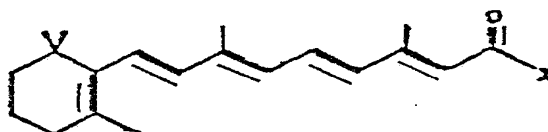
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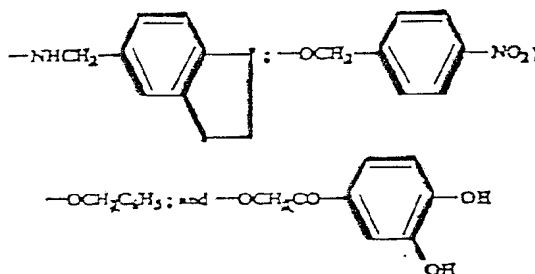
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What is claimed is:

1. A method for increasing the rate of growth of hair, prolonging the anagen phase of the hair cycle and treating various types of alopecias by administering to a mammal, a retinoid or a pharmaceutically acceptable ester, ether or derivative or retinoid analogue or polyene thereof, in an amount effective for the purpose in combination with minoxidil (2,4-diamino-6-piperidino-pyrimidine-3-oxide) or its active derivatives or analogues or other compounds which act to increase vascularity and are vasodilators.
2. The method of Claim 1 wherein the retinoid is all-trans retinoic acid or retinaldehyde or all-trans retinoic acetate, or other suitable esters or ethers or salts of retinoic acid or retinoid analogues or polyenes.
3. The method of Claim 1 wherein the retinoid is selected from the group consisting of the stereoisomers of vitamin A acid, or vitamin A<sub>2</sub> acid,  $\gamma$ -vitamin A acid,  $\alpha$ -vitamin A acid, 5,6 epoxy-vitamin A acid, dehydrovitamin acid, anhydrovitamin A acid or the aldehydes, alcohols, esters, ethers or stereoisomers or analogues or derivatives of the above mentioned compounds.
4. The method of Claim 1 wherein the retinoid is a naturally occurring metabolite of vitamin A or vitamin A acid such as 4-hydroxy retinoic acid, 4-keto retinoic acid, 4-oxo-retinoic acid, 5,8 oxy-retinoic acid or stereoisomers of the above mentioned compounds or aldehydes or derivatives such as esters or analogues or polyenes.
5. The method of Claim 1 wherein the retinoid analog is:



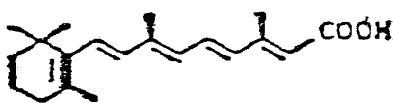
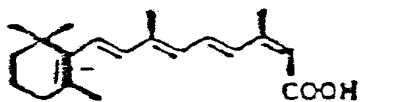
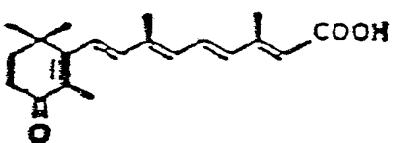
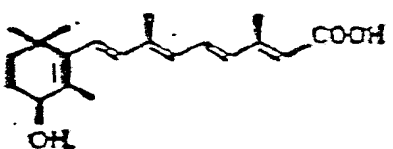
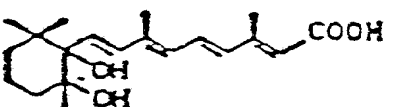
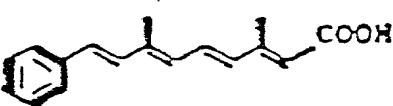
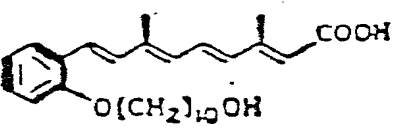
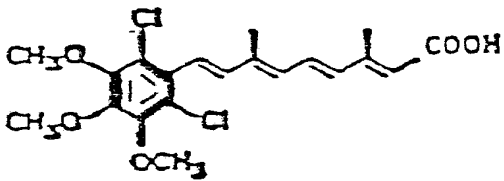
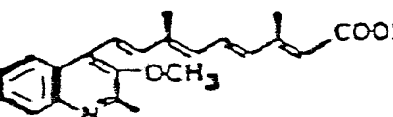
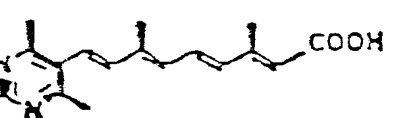
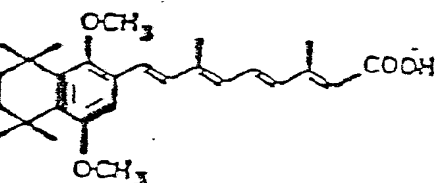
wherein X is a member selected from the group consisting of:  
 $-\text{OCH}_2\text{CONH}_2$ ; mixed  $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3$  and  $-\text{OCH}(\text{CH}_3)\text{CH}_2\text{OH}$ ;  $-\text{OCH}_2\text{CH}_2\text{OH}$ ;

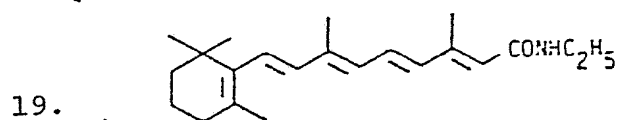
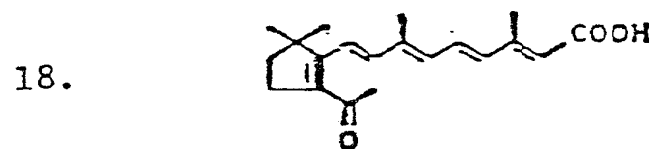
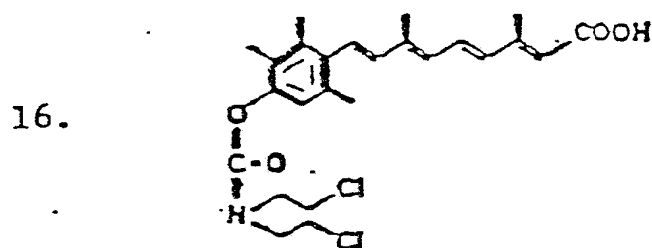
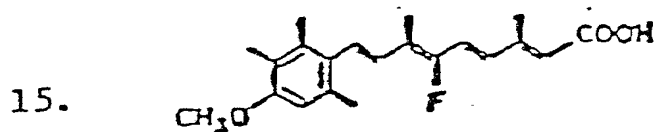
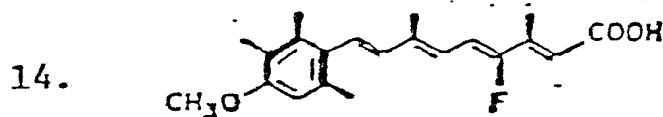
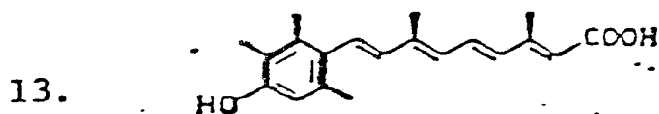
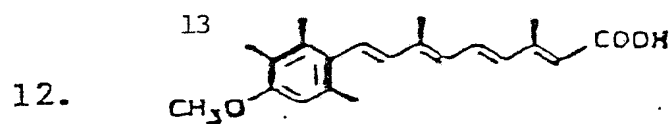


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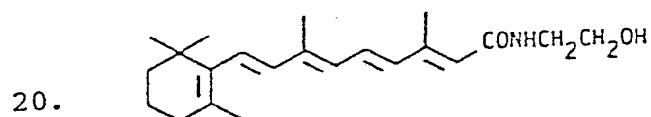


6. The method of Claim 1<sup>12</sup> wherein the retinoid analog is selected from the group listed below:

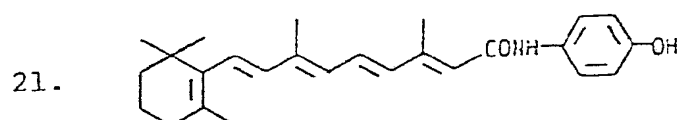
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Retinoic Acid Ethyl Amide



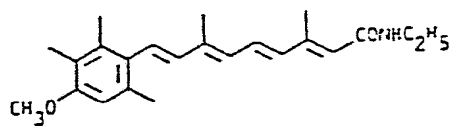
Retinoic Acid 2-Hydroxyethyl Amide



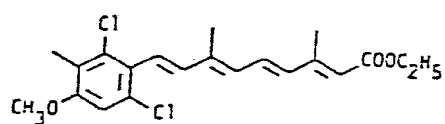
Retinoic Acid *p*-Hydroxyphenyl Amide

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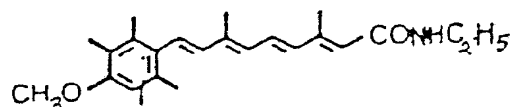
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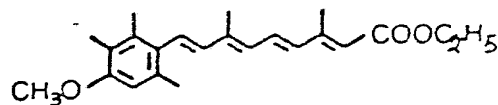


7. The method of Claim 1 wherein the retinoid analog is selected from the group listed below:

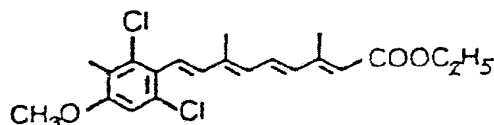
Trimethylmethoxyphenyl (TMMP)  
analog of retinoic acid ethyl amide  
(Molrelinid)



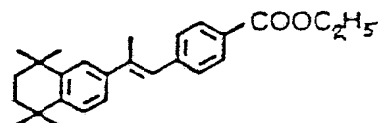
Trimethylmethoxyphenyl (TMMP)  
analog of retinoic acid ethyl ester  
(Etreteinate)



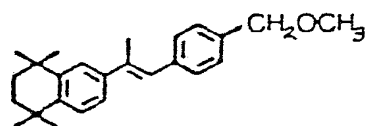
Dichloromethylmethoxyphenyl (DCMMP)  
analog of retinoic acid ethyl ester



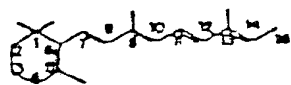
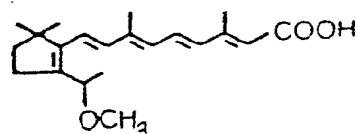
Arolinoid ethyl ester



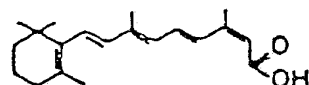
Arolinoid methyl ether



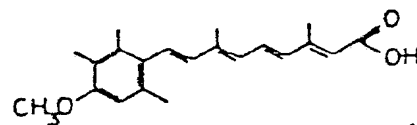
1-Methoxyethyl-cyclopentenyl  
analog of retinoic acid



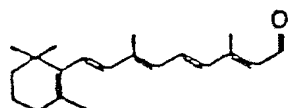
Axerophthene



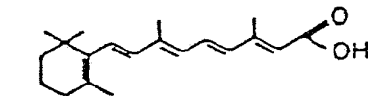
13-cis-Retinoic acid



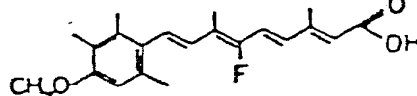
Trimethylmethoxyphenyl  
(TMMP) analog of RA



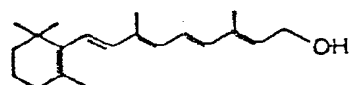
Retinol



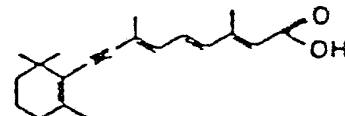
$\beta$ -all-trans-Retinoic acid (RA)



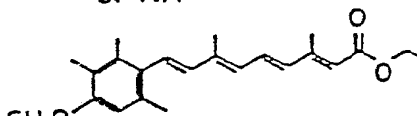
10-Fluoro-TMMP analog  
of RA



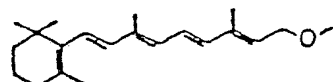
Retinol



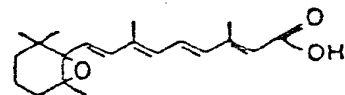
7,8-Dehydro analog  
of RA



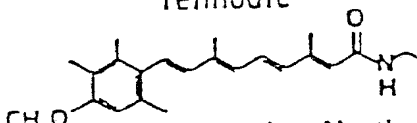
TMMP analog of ethyl  
retinoate



Retinyl methyl ether

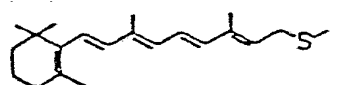


5,6-Epoxy analog of RA

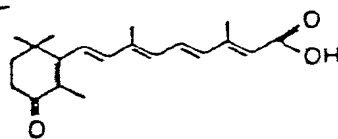


TMMP analog N-ethyl-  
retinamide

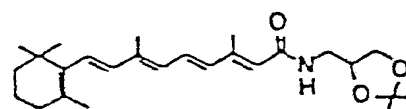
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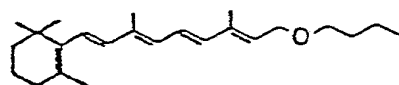
Retinyl methyl thioether



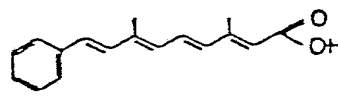
4-Oxo analog of RA



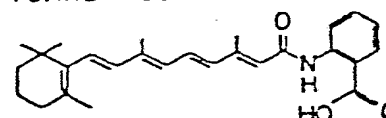
N-Methyl-dimethyldioxolan-retinamide



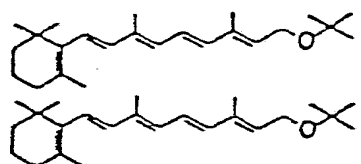
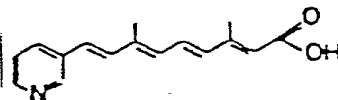
Retinyl n-butyl ether



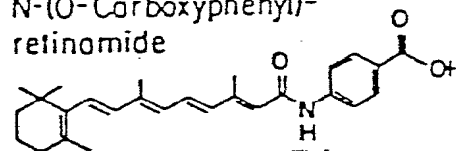
Phenyl analog of RA



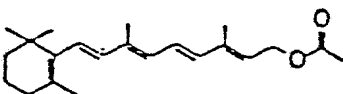
N-(O-Carboxyphenyl)-retinamide

Retinyl *tert*-butyl ether

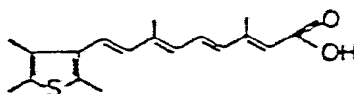
Pyridyl analog of RA



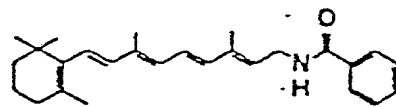
N-(p-Carboxyphenyl)-retinamide



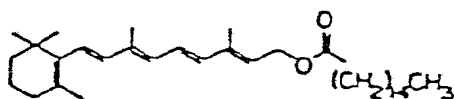
Retinyl acetate



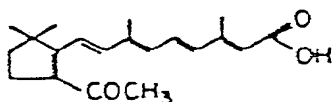
Trimethylthiophene (TMT) N-Benzoyl-retinylamine analog of RA



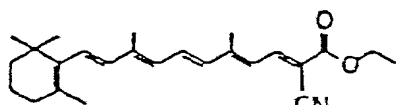
N-Benzoyl-retinylamine



Retinyl palmitate

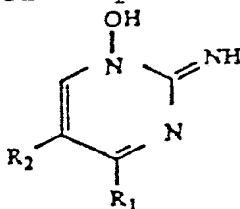


Dimethylacetyl cyclo-

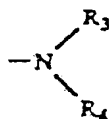


Retinylidene ethylcyano-

8. The method of Claim 1 wherein the 6-amino-4 (substituted amino)-1,2 dihydro-1-hydroxy-2-iminopyrimidine compounds (minoxidil and derivatives and analogues) are selected from the group of compounds having the basic formula:



wherein  $R_1$  is a moiety selected from the group consisting of moieties of the formula



wherein  $R_3$  and  $R_4$  are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together  $R_3$  and  $R_4$  may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino, and 4-lower-alkylpiperazinyl, each of said hetero cyclic moieties having attached as substituents on the carbon atoms 0-3 lower alkyl groups, hydroxy or alkoxy wherein  $R_2$  is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxy-alkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkaralkyl, lower alkoxyaralkyl, and lower haloaralkyl and the pharmacologically acceptable acid addition salts thereof as well as addition products such as sulfate forms or more lipophilic derivatives thereof.

9. The method of Claim 1 wherein the alopecias are of the following types: male pattern baldness (androgenetic), diffuse hair loss, alopecia areata and non-specific hair loss.

10. The method of Claim 1 in which the retinoid compounds or analogues or derivatives of retinoids such as polyenes described in Claims 5, 6 and 7 are used alone or with other compounds which act to increase vascularity in the area of the pilosebaceous unit.

11. The method of Claim 1 wherein the mammal is a human and the hair is scalp hair.

12. The method of Claim 1 wherein the retinoid concentration in the topical lotion, cream, ointment, conditioner or shampoo is between 0.0001 and 5% by weight, and the minoxidil or minoxidil derivative or other compound which promotes vasodilation is between 0.01 to 30% by weight.

13. The method of Claim 1 wherein the minoxidil and retinoid compositions are given orally in a dosage of between 0.0001 to 20 mg/kg of body weight of a mammal.

SUBSTITUTE SHEET



## AMENDED CLAIMS

[received by the International Bureau on 28 March 1983 (28.03.83);  
original claims 1 to 13 have been replaced by the amended claims 1 to 13]

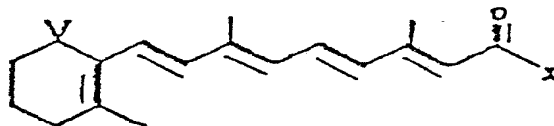
1. A composition useful for increasing the rate of growth of hair, for prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising of a retinoid or a pharmaceutically acceptable ester, ether or derivative or retinoid analogue or polyene thereof, in a synergistic combination with minoxidil (2,4-diamino-6-piperidino-pyrimidine-3-oxide) or its active derivatives or analogues, optionally composing additional other compounds which act to increase vascularity and are vasodilators.

2. A composition as claimed in Claim 1 wherein the retinoid is all-trans retinoic acid or retinaldehyde or all-trans retinoic acetate, or other suitable esters or ethers or salts of retinoic acid or retinoid analogues or polyenes.

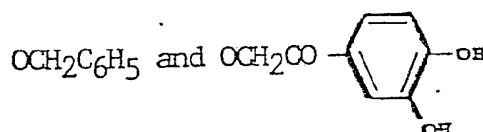
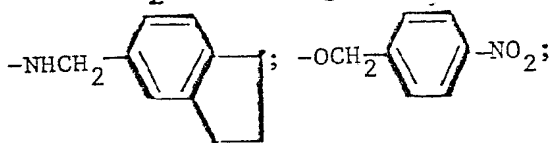
3. A composition as claimed in Claim 1 wherein the retinoid is selected from the group consisting of the stereoisomers of vitamin A acid or vitamin A<sub>2</sub> acid,  $\gamma$ -vitamin A acid,  $\alpha$ -vitamin A acid, 5,6 epoxy-vitamin A acid, dehydrovitamin acid, anhydro-vitamin A acid or the aldehydes, alcohols, esters, ethers or stereoisomers or analogues or derivatives of the above mentioned compounds.

4. A composition as claimed in Claim 1 wherein the retinoid is a naturally occurring metabolite of vitamin A or vitamin A acid such as 4-hydroxy retinoic acid, 4-keto retinoic acid, 4-oxo-retinoic acid, 5,8 oxy-retinoic acid or stereoisomers of the above mentioned compounds or aldehydes or derivatives such as esters or analogues or polyenes.

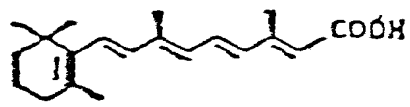
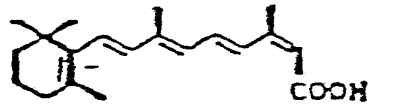
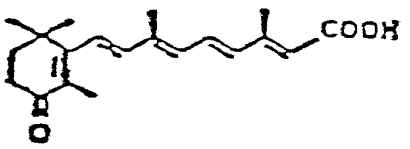
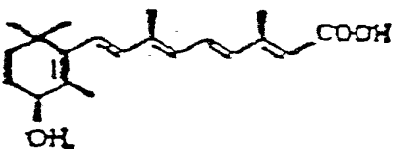
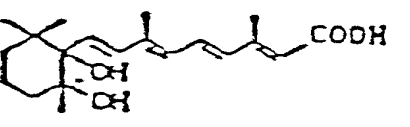
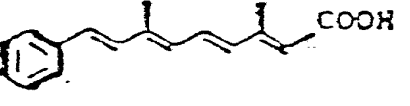
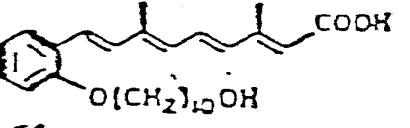
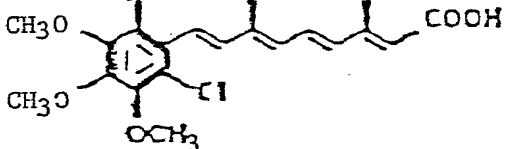
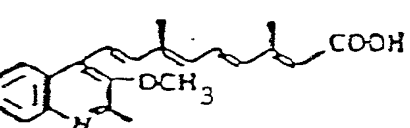
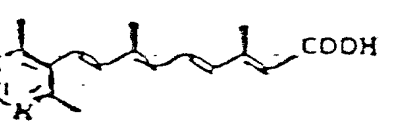
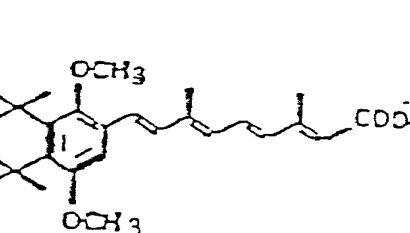
5. A composition as claimed in Claim 1 wherein the retinoid analog is:



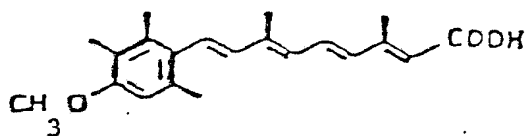
wherein X is a member selected from the group consisting of:  
-OCH<sub>2</sub>CONH<sub>2</sub>; mixed - OCH<sub>2</sub>CH(OH)CH<sub>3</sub> and - OCH(CH<sub>3</sub>)CH<sub>2</sub>OH; -OCH<sub>2</sub>CH<sub>2</sub>OH;



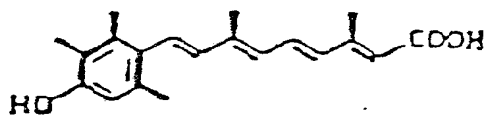
6. A composition as claimed in Claim 1 wherein the retinoid analog is selected from the group listed below:

1. 
2. 
3. 
4. 
5. 
6. 
7. 
8. 
9. 
10. 
11. 

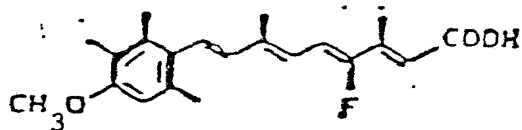
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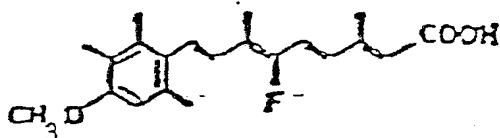
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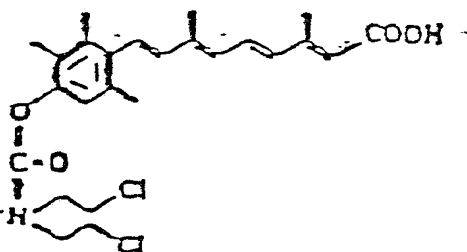
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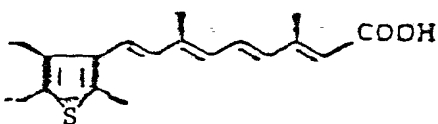
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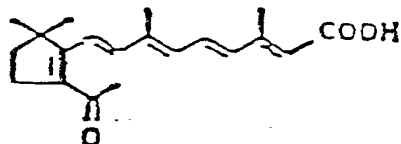
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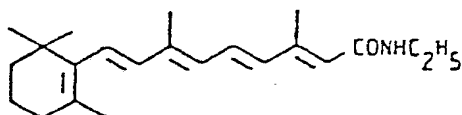
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18.

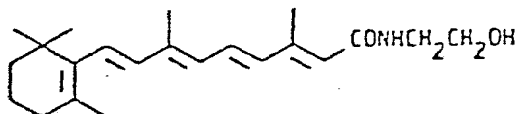


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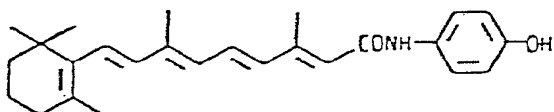
Retinoic Acid Ethyl Amide

20.



Retinoic Acid 2-Hydroxyethyl Amide

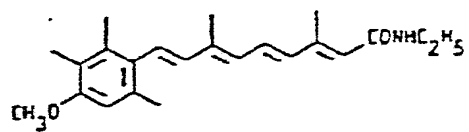
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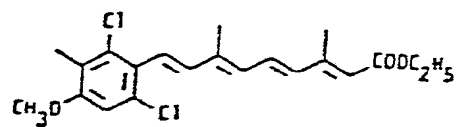
Retinoic Acid p-Hydroxyphenyl Amide

- 22 -

22.



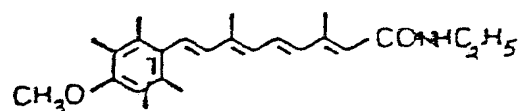
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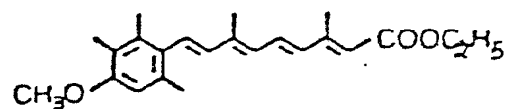


7. A composition as claimed in Claim 1 wherein the retinoid analog is selected from the group listed below:

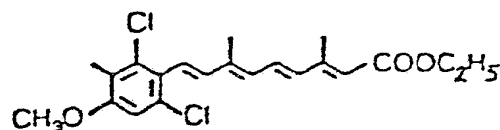
Trimethylmethoxyphenyl (TMMP)  
analog of retinoic acid ethyl amide  
(Molrelinid)



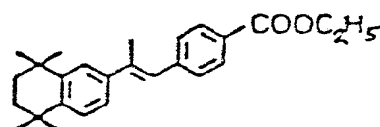
Trimethylmethoxyphenyl (TMMP)  
analog of retinoic acid ethyl ester  
(Etretrate)



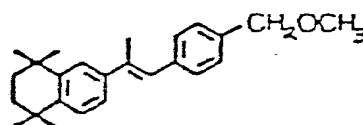
Dichloromethylmethoxyphenyl (DCMMP)  
analog of retinoic acid ethyl ester



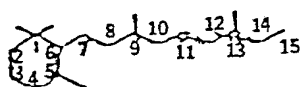
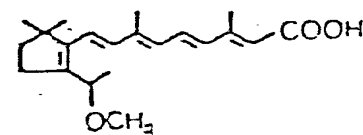
Arotinoid ethyl ester



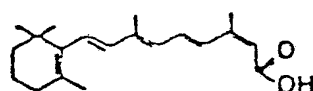
Arotinoid methyl ether



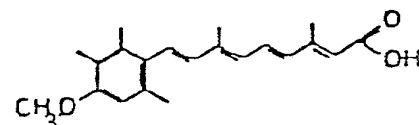
1-Methoxyethyl-cyclopentenyl  
analog of retinoic acid



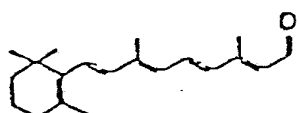
Axerophthene



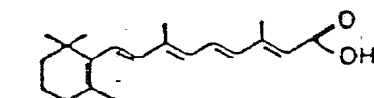
13-cis-Retinoic acid



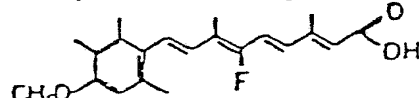
Trimethylmethoxyphenyl  
(TMMP) analog of RA



Retinol



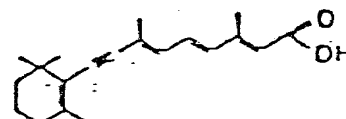
$\beta$ -all-trans-Retinoic acid (RA)



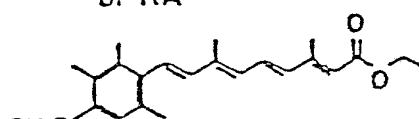
10-Fluoro-TMMP analog  
of RA



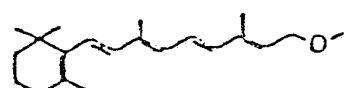
Retinol



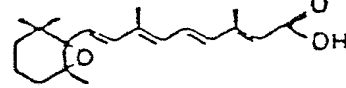
7,8-Dehydro analog  
of RA



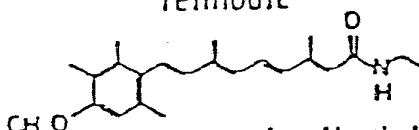
TMMP analog of ethyl  
retinoate



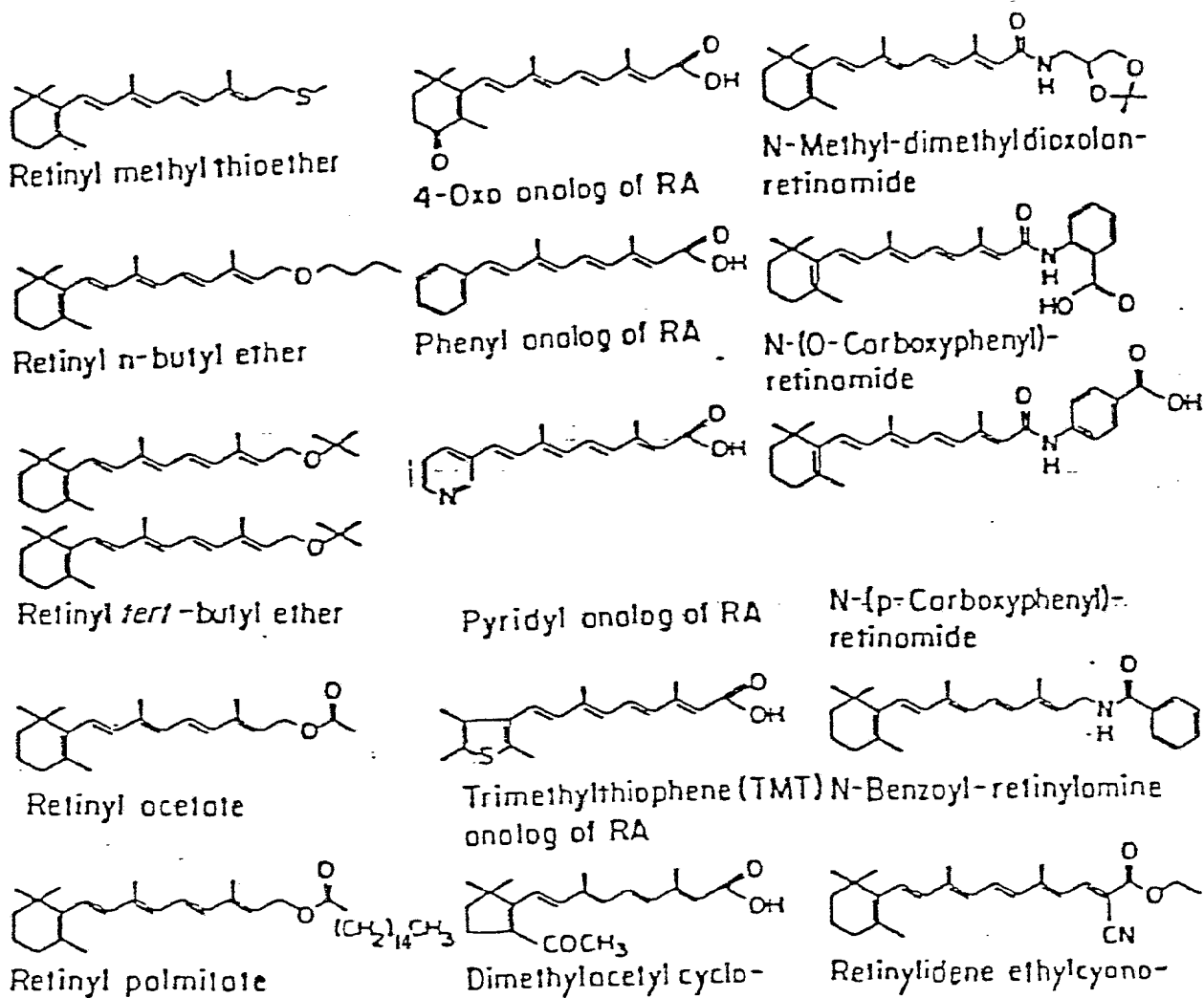
Retinyl methyl ether



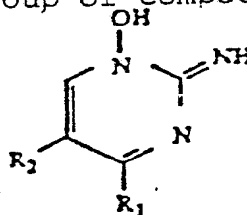
5,6-Epoxy analog of RA



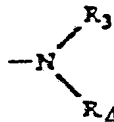
TMMP analog N-ethyl-  
retinamide



8. A composition as claimed in Claim 1 wherein the 6-amino-4 (substituted amino)-1,2 dihydro-1-hydroxy-2-iminopyrimidine compounds or minoxidil and its derivatives and analogues can be used. The group of compounds can have the basic formula:



wherein  $R_1$  is a moiety selected from the group consisting of moieties of the formula



wherein  $R_3$  and  $R_4$  are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together  $R_3$  and  $R_4$  may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidiny, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino, and 4-lower-alkylpiperazinyl, each of said hetero cyclic moieties having attached as substituents on the carbon atoms 0-3 lower alkyl groups, hydroxy or alkoxy wherein  $R_2$  is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkaralkyl, lower alkoxyaralkyl, and lower haloaralkyl and the pharmacologically acceptable acid addition salts thereof. Addition products such as sulfate forms or more lipophilic derivatives of minoxidil are also included.

9. A composition of matter composed of a retinoid derivative useful for increasing the rate of hair growth on the scalp.

10. A composition as claimed in Claim 9 in which the retinoid compounds or analogues or derivatives of retinoids such as polyenes as described in Claims 5, 6 and 7 are used alone or with other compounds which act to increase vascularity in the area of the pilosebaceous unit.



11. The composition of Claim 1 wherein the mammal is a human and the hair is scalp hair.

12. The composition of Claim 1 wherein the retinoid concentration in the topical lotion, cream, ointment, conditioner or shampoo is between 0.0001 and 5% by weight, and the minoxidil or minoxidil derivative or other compounds which promotes vasodilation is between 0.01 to 30% by weight.

13. The composition of Claim 1 wherein the minoxidil and retinoid compositions are given orally in a dosage of between 0.0001 to 20 mg/kg of body weight of a mammal.



# INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/01593

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>3</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. <sup>3</sup> A61K 7/06; A61K 31/505		
U.S. Cl. 424/70; 424/305		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>4</sup>		
Classification System	Classification Symbols	
U.S.	424/70, 251	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup>		
Category *	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
X	U.S., A, 3,759,978, Published 18 September, 1973, Column 10, lines 27-34.	1-13
X	U.S., A, 3,931,279, Published 06 January, 1976, Column 2, lines 38-70.	1-13
X	U.S., A, 3,954,835, Published 04 May, 1976, Column 6, lines 27-47.	1-13
X	U.S., A, 4,126,698, Published 21 November, 1978, Column 1, lines 35-65.	1-13
<p>* Special categories of cited documents: <sup>15</sup></p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document cited for special reason other than those referred to in the other categories</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> </div> <div style="width: 45%;"> <p>"P" document published prior to the international filing date but on or after the priority date claimed</p> <p>"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search <sup>2</sup>	Date of Mailing of this International Search Report <sup>2</sup>	
16 February 1983	24 FEB. 1983	
International Searching Authority <sup>1</sup>	Signature of Authorized Officer <sup>20</sup>	
ISA/U.S.	DALE R. ORE	